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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/830,968	11/06/2001	Carlos Miguel Carcagno	1909.0040002	7301

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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/830,968	CARCAGNO ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,7-13,16 and 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-5, 7-13, 16 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner in this application has changed. Please direct future correspondences to Examiner Michael C. Wilson, Art Unit 1632.

Applicant's arguments filed 11-6-08 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 2, 6, 14, 15, 17-19, 21 and 22 have been canceled. Claims 1, 3-5, 7-13, 16 and 20 remain pending.

Claim Rejections - 35 USC § 112

New Matter

Claims 1, 3-5, 7-13, 16 and 20 remain rejected under 35 U.S.C. 112, first paragraph, new matter.

Culture media 3 disclosed in the specification on pg 14 consist of DMEM (Dulbecco's modified Eagle's medium), F12 medium, insulin, $NaHCO_3$, glucose, lactose, galactose, ethanolamine, sodium pyruvate and glutamine, tryptophan, asparagines, and serine".

The scope of "pyruvate" as now broadly claimed was not contemplated in the specification as originally filed. Support has not been provided for the breadth of this reagent now claimed and none can be found in the specification as originally filed.

Culture Medium no. 3
Basal Culture Medium + Insulin

ISCOVE'S DNEM	8.85 g/l	Tryptophan	27mg/l
HAM F12	5.35 g/l	Asparagine	40mg/l
$NaHCO_3$	2.10 g/l	Serine	80mg/l
Glucose	1.30 g/l	Ethanolamine	3mg/l
Lactose	0.20 g/l	Glutamine	0.20 mg/l
Galactose	0.20 g/l	Sodium Pyruvate	0.11 g/l
Glutamine	1.90 g/l	Insulin	10 mg/l

Enablement

Claims 1, 3-5, 7-13, 16 and 20 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the reason of record as set forth in the office action mailed on 03/21/07.

The claims are drawn to a method of obtaining human erythropoietin by culturing mammalian cells selected from the group consisting of CHO, COS, BHK, Namalwa, and HeLa cells that express recombinant human erythropoietin in culture medium consisting of DMEM (Dulbecco's modified Eagle's medium), F12 medium, insulin, $NaHCO_3$, glucose, lactose, galactose, ethanolamine, sodium pyruvate and glutamine, tryptophan, asparagines, and serine. The claims encompass obtaining EPO by culturing CHO, COS, BHK, Namalwa or HeLa cells using Culture Medium 3 alone.

The state of art at the time of filing teaches various factors affect the production of recombinant proteins in serum free medium. Several culture parameters could affect the metabolism of cultured cells and hence affect the glycosylation and sialylation of secreted glycoproteins. These factors include combination of nutrition, concentration and accumulation of by products. (Wang, Biotechnol Bioeng. 77(2):194-203. 2002; Yang, Biotechnol Prog. 18(1):129-38., 2002; Schroder, J Biotechnol. 108(3):279-92, 2004). For example, recombinant production of EPO could be best achieved by using a basal medium prepared by supplementing Iscove's modified Dulbecco's medium (IMDM) with Fe(NO3)3.9H2O, CuCl2 and ZnSO4.7H2O along with Insulin, transferrin

and ethanolamine in optimal concentrations (Lee, J Biotech. 69:85-93, 1999. ref of record). Therefore the combination of essential nutrients (sugars, salts and growth factors etc) and their concentration varies not only with choice of host cells but also depends upon the selection of culture conditions.

The culture media claimed correlates most closely to Culture Medium 3 (pg 14).

Example 1 teaches culturing CHO transfected with a vector encoding human EPO in Culture Medium 1, removing Medium 1, and then adding Medium 2. Example 2 teaches expanding cells from Example 1 in Medium 2. Example 3 teaches expanding cells from Example 2 in Medium 1. Example 4 teaches expanding cells from Example 3 in Medium 1. Example 5 teaches expanding cells from Example 4 in Medium 1. Example 6 teaches expanding cells from Example 5 in Medium 1. Example 7 teaches harvesting supernatant from the cell culture of Example 6 every 48 hours and replacing it with Culture Medium 3 (pg 10). This procedure was repeated 5 times per flask. The harvested supernatants were concentrated and EPO was recovered. Each of the 5 harvests resulted in functional EPO (pg 11).

Overall, the specification teaches the specification teaches a method of obtaining human EPO by culturing CHO transfected with a vector encoding human EPO in culture medium comprising fetal calf serum, expanding the cells in culture medium comprising calf serum, harvesting supernatant from the cells every 48 hours and replacing it with Culture Medium 3; repeating the harvesting 5 times; concentrating the harvested supernatants; and recovering the human EPO from the harvested supernatants.

The specification does not enable culturing cells expressing recombinant human EPO using Culture Medium 3 alone as encompassed by the claims. The specification is limited to sequential culture conditions that sustain the growth and proliferation of CHO cells to produce EPO. The USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of skill. The state of the art clearly teaches that adaptation of cell lines to serum free conditions is critical step in order to sustain viability and growth of recombinant cells, which not only requires stepwise weaning of serum conditions but also the addition of various additives to the culture media in order to produce a particular recombinant protein of interest. The specification does not overcome the unpredictability in the art by teaching how to culture cells in the presence of Culture Medium 3 alone as encompassed by the claims such that the cells would live and express functional EPO for harvest. Without such guidance, it would have required those of skill undue experimentation to determine how to use Culture Medium 3 alone as encompassed by the claims to harvest recombinant human EPO from cells.

The specification fails to correlate the culture conditions obtained with CHO cells to COS, BHK, Namalwa and HeLa cells. It is unclear that serum free culture conditions of CHO cells after expansion in medium with fetal calf serum would also allow COS, BHK, Namalwa and HeLa to express functional human EPO. The USPTO does not

have laboratory facilities to test if COS, BHK, Namalwa and HeLa will express functional EPO after serum free culture conditions as found with EPO; therefore, the issues is raised based on the state of knowledge pertinent to an art at the time of the invention. The state of the art clearly teaches that adaptation of a cell line to serum free conditions is critical step in order to sustain viability and growth of recombinant cells, which not only requires stepwise weaning of serum conditions but also the addition of various additives to the culture media in order to produce a particular recombinant protein of interest. The specification does not overcome the unpredictability in the art by correlating the results obtained with CHO cells expanded in culture medium containing fetal calf serum, then harvested in Medium 3 (Example 7) to COS, BHK, Namalwa and HeLa cells such that COS, BHK, Namalwa and HeLa cells would be expected to live and express functional EPO for harvest. Without such guidance, it would have required those of skill undue experimentation to determine how to obtain the results obtained with CHO cells in COS, BHK, Namalwa and HeLa as claimed.

While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.

Applicants' arguments regarding the references cited by the examiner are noted but are not persuasive. The references clearly establish the culture conditions required to obtain recombinant EPO expression in serum free culture medium alone were unpredictable.

Indefiniteness

The rejection of claims 1, 3-5, 7-13, 16 and 20 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention has been withdrawn.

Double Patenting

Claims 1, 3-5, 7-13, 16 and 20 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 7-13 of U.S. Patent No. 6,777,205, for the same reasons of record of record. The applicant states that to advance prosecution, Applicants will submit a terminal disclaimer in accordance with 37 C.F.R. § 1.321(c) upon the notification by the Examiner of allowable subject matter

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claims are allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson

/Michael C. Wilson/
Patent Examiner